

Claims

1. A pharmaceutical composition comprising (i) one or more genetically engineered microorganisms, said microorganisms comprising a nucleic acid encoding a protein that breaks down interstitial matrix or targets tumor vasculature; and (ii) a pharmaceutically acceptable carrier.
2. The pharmaceutical composition of claim 1, wherein said nucleic acid encodes a protein selected from the group consisting of a matrix degrading protein, matrix metalloproteinases (MMPs), a protein that increases MMP production, a protein that increases collagen turnover, a protein that decreases collagen formation, a protein that increases extracellular matrix (ECM) turnover, a protein that decreases ECM formation, relaxin, collagenase, anti-fibrotic proteins, halofuginone, hyaluronidase, chondroitinase, heparatinase, and a cathepsin enzyme.
3. The pharmaceutical composition of claim 1, wherein said microorganism is a virus or a bacterium.
4. The pharmaceutical composition of claim 3, wherein said virus is selected from the group consisting of a replication defective virus, a replication selective virus, a replication competent virus, and an oncolytic virus.
5. The pharmaceutical composition of claim 4, wherein said virus is a member of a virus family selected from the group consisting of: herpesviruses, adenoviruses, adeno-associated viruses, lentiviruses, parvoviruses, papovaviruses, poxviruses, hepadnaviruses, alphaviruses, iridoviruses, alphaviruses, and retroviruses.

6. The pharmaceutical composition of claim 5, wherein said virus is a herpes simplex virus-1 comprising a mutation in a ribonucleotide reductase gene, wherein said mutation results in inactivation of said ribonucleotide reductase gene.

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7. The pharmaceutical composition of claim 5, wherein said virus is an adenovirus comprising a mutation in the E1A CR-2 gene, wherein said mutation results in inactivation of said E1A CR-2 gene.

10 8. The pharmaceutical composition of claim 3, wherein said bacteria are selected from the group consisting of: *Salmonella bacteriophage*, *S. bongori*, *S. choleraesuis*, *S. enterica*, *S. enteritidis*, *S. paratyphi*, *S. typhi*, *S. typhimurium*, *S. typhimurium bacteriophage*, *Shigella boydii*, *S. dysenteriae*, *S. flexneri*, *S. sonnei*, *Staphylococcus arlettae*, *S. aureus*, *S. auricularis*, *S. bacteriophage*, *S. capitis*, *S. caprae*, *S. carnosus*, *S. caseolyticus*, *S. chromogenes*, *S. cohnii*, *S. delphini*, *S. epidermidis*, *S. equorum*, *S. felis*, *S. fleurettii*, *S. gallinarum*, *S. haemolyticus*, *S. hominis*, *S. hyicus*, *S. intermedius*, *S. kloosii*, *S. lentus*, *S. lugdunensis*, *S. lutrae*, *S. muscae*, *S. mutans*, *S. pasteurii*, *S. phage*, *S. piscifermentans*, *S. pulvereri*, *S. saccharolyticus*, *S. saprophyticus*,
15 *S. schleiferi*, *S. sciuri*, *S. simulans*, *S. succinus*, *S. vitulinus*, *S. warneri*, *S. xylosus*, *Yersinia aldovae*, *Y. bercovieri*, *Y. enterocolitica*, *Y. frederiksenii*, *Y. intermedia*, *Y. kristensenii*, *Y. mollaretii*, *Y. pestis*, *Y. philomiragia*, *Y. pseudotuberculosis*, *Y. rohdei*, and *Y. ruckeri*, *Bifidobacterium adolescentis*, *B. animalis*, *B. bifidum*, *B. boum*, *B. breve*, *B. coryneforme*, *B. dentium*, *B. indicum*, *B. infantis*, *B. longum*, *B. magnum*, *B. pseudolongum*, *Lactobacillus bifidus*, *L. delbrueckii*, *Clostridium absonum*, *C. acetobutylicum*, *C. beijerinckii*, *C. bifermentans*, *C. butyricum*, *C. difficile*, *C. histolyticum*, *C. novyi*, *C. oncolyticum*, *C. pectinovorum*, *C. perfringens*, *C. sordelli*, *C. tetani*, *C. tyrobutyricum*, and *Corynebacterium parvum*,

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9. A kit comprising (i) one or more genetically engineered microorganisms, said microorganisms comprising a nucleic acid encoding a protein that breaks down the interstitial matrix or targets the tumor vasculature, and (ii) instructions for their use for treating a cancer in a mammal.

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10. The kit of claim 9, wherein said nucleic acid encodes a protein selected from the group consisting of a matrix degrading protein, matrix metalloproteinases (MMPs), a protein that increases MMP production, a protein that increases collagen turnover, a protein that decreases collagen formation, a protein that increases extracellular matrix (ECM) turnover, a protein that decreases ECM formation, relaxin, collagenase, anti-fibrotic proteins, halofuginone, hyaluronidase, chondroitinase, heparatinase, and a cathepsin enzyme.

15 11. The kit of claim 9, wherein said microorganism is a virus or a bacterium.

12. The kit of claim 11, wherein said virus is selected from the group consisting of a replication defective virus, a replication selective virus, a replication competent virus, and an oncolytic virus.

20 13. The kit of claim 12, wherein said virus is a member of a virus family selected from the group consisting of: herpesviruses, adenoviruses, adeno-associated viruses, lentiviruses, parvoviruses, papovaviruses, poxviruses, 25 hepadnaviruses, alphaviruses, iridoviruses, and retroviruses.

14. The kit of claim 13, wherein said virus is a herpes simplex virus-1 comprising a mutation in a ribonucleotide reductase gene, wherein said mutation results in inactivation of said ribonucleotide reductase gene.

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15. The kit of claim 13, wherein said virus is an adenovirus comprising a mutation in the E1A CR-2 gene, wherein said mutation results in inactivation of said E1A CR-2 gene.

- 5 16. The kit of claim 9, wherein said bacterium is selected from the group consisting of: *Salmonella bacteriophage*, *S. bongori*, *S. choleraesuis*, *S. enterica*, *S. enteritidis*, *S. paratyphi*, *S. typhi*, *S. typhimurium*, *S. typhimurium bacteriophage*, *Shigella boydii*, *S. dysenteriae*, *S. flexneri*, *S. sonnei*, *Staphylococcus arlettae*, *S. aureus*, *S. auricularis*, *S. bacteriophage*, *S. capitis*,
10 *S. caprae*, *S. carnosus*, *S. caseolyticus*, *S. chromogenes*, *S. cohnii*, *S. delphini*, *S. epidermidis*, *S. equorum*, *S. felis*, *S. fleurettii*, *S. gallinarum*, *S. haemolyticus*, *S. hominis*, *S. hyicus*, *S. intermedius*, *S. kloosii*, *S. lentus*, *S. lugdunensis*, *S. lutrae*, *S. muscae*, *S. mutans*, *S. pasteurii*, *S. phage*, *S. piscifermentans*, *S. pulvereri*, *S. saccharolyticus*, *S. saprophyticus*, *S. schleiferi*, *S. sciuri*, *S.*
15 *simulans*, *S. succinus*, *S. vitulinus*, *S. warneri*, *S. xylosus*, *Yersinia aldovae*, *Y. bercovieri*, *Y. enterocolitica*, *Y. frederiksenii*, *Y. intermedia*, *Y. kristensenii*, *Y. mollaretii*, *Y. pestis*, *Y. philomiragia*, *Y. pseudotuberculosis*, *Y. rohdei*, and *Y. ruckeri*, *Bifidobacterium adolescentis*, *B. animalis*, *B. bifidum*, *B. boum*, *B. breve*, *B. coryneforme*, *B. dentium*, *B. indicum*, *B. infantis*, *B. longum*, *B.*
20 *magnum*, *B. pseudolongum*, *Lactobacillus bifidus*, *L. delbrueckii*, *Clostridium absonum*, *C. acetobutylicum*, *C. beijerinckii*, *C. bifermentans*, *C. butyricum*, *C. difficile*, *C. histolyticum*, *C. novyi*, *C. oncolyticum*, *C. pectinovorum*, *C. perfringens*, *C. sordelli*, *C. tetani*, *C. tyrobutyricum*, and *Corynebacterium parvum*.

17. A method of treating a cancer in a mammal, said method comprising administering to said mammal one or more genetically engineered microorganisms, said microorganism comprising a nucleic acid encoding a protein that breaks down the interstitial matrix or targets the tumor vasculature, wherein said administering is for a time and in an amount sufficient to destroy, slow, or arrest said cancer.

18. The method of claim 17, wherein said nucleic acid encodes a protein selected from the group consisting of a matrix degrading protein, matrix metalloproteinases (MMPs), a protein that increases MMP production, a protein that increases collagen turnover, a protein that decreases collagen formation, a protein that increases extracellular matrix (ECM) turnover, a protein that decreases ECM formation, relaxin, collagenase, anti-fibrotic proteins, halofuginone, hyaluronidase, chondroitinase, heparatinase, and a cathepsin enzyme.

19. The method of claim 17, wherein said microorganism is a virus or a bacterium.

20. The method of claim 19, wherein said virus is selected from the group consisting of a replication defective virus, a replication selective virus, a replication competent virus, and an oncolytic virus.

21. The method of claim 20, wherein said said virus is a member of a virus family selected from the group consisting of: herpesviruses, adenoviruses, adeno-associated viruses, lentiviruses, parvoviruses, papovaviruses, poxviruses, hepadnaviruses, alphaviruses, iridoviruses, and retroviruses.

22. The method of claim 21, wherein said virus is a herpes simplex virus-1 comprising a mutation in a ribonucleotide reductase gene, wherein said mutation results in inactivation of said ribonucleotide reductase gene.

5 23. The method of claim 21, wherein said virus is an adenovirus comprising a mutation in the E1A CR-2 gene, wherein said mutation results in inactivation of said E1A CR-2 gene.

24. The method of claim 19, wherein said bacterium is selected from
 10 the group consisting of: *Salmonella bacteriophage*, *S. bongori*, *S. choleraesuis*,
S. enterica, *S. enteritidis*, *S. paratyphi*, *S. typhi*, *S. typhimurium*, *S. typhimurium*
bacteriophage, *Shigella boydii*, *S. dysenteriae*, *S. flexneri*, *S. sonnei*,
Staphylococcus arlettae, *S. aureus*, *S. auricularis*, *S. bacteriophage*, *S. capitis*,
S. caprae, *S. carnosus*, *S. caseolyticus*, *S. chromogenes*, *S. cohnii*, *S. delphini*,
 15 *S. epidermidis*, *S. equorum*, *S. felis*, *S. fleurettii*, *S. gallinarum*, *S. haemolyticus*,
S. hominis, *S. hyicus*, *S. intermedius*, *S. kloosii*, *S. lentus*, *S. lugdunensis*, *S.*
lutrae, *S. muscae*, *S. mutans*, *S. pasteurii*, *S. phage*, *S. piscifermentans*, *S.*
pulvereri, *S. saccharolyticus*, *S. saprophyticus*, *S. schleiferi*, *S. sciuri*, *S.*
simulans, *S. succinus*, *S. vitulinus*, *S. warneri*, *S. xylosus*, *Yersinia aldovae*, *Y.*
 20 *bercovieri*, *Y. enterocolitica*, *Y. frederiksenii*, *Y. intermedia*, *Y. kristensenii*, *Y.*
mollaretii, *Y. pestis*, *Y. philomiragia*, *Y. pseudotuberculosis*, *Y. rohdei*, and *Y.*
ruckeri, *Bifidobacterium adolescentis*, *B. animalis*, *B. bifidum*, *B. boum*, *B.*
breve, *B. coryneforme*, *B. dentium*, *B. indicum*, *B. infantis*, *B. longum*, *B.*
magnum, *B. pseudolongum*, *Lactobacillus bifidus*, *L. delbrueckii*, *Clostridium*
 25 *absonum*, *C. acetobutylicum*, *C. beijerinckii*, *C. bifermentans*, *C. butyricum*, *C.*
difficile, *C. histolyticum*, *C. novyi*, *C. oncolyticum*, *C. pectinovorum*, *C.*
perfringens, *C. sordelli*, *C. tetani*, *C. tyrobutyricum*, and *Corynebacterium*
parvum.

25. The method of claim 17, furthering comprising administering a therapy selected from the group consisting of a chemotherapeutic agent, radiation therapy, an anti-angiogenic compound, an anti-vascular agent, an oncolytic virus.

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26. The method of claim 17, wherein said mammal is a human.